Patentability Under 35 U.S.C. §102

Claims 1-5 and 7 stand rejected under 35 U.S.C. §102(b) as allegedly anticipated by Hussain et al. (WO Patent Number 82/03768 or equivalent U.S. Patent Number 4,464,378 ('378 patent)), for reasons stated in the prior Office Action (Paper Number 6, mailed April 25, 2000). Briefly, the Office states that Hussain '378 discloses a "pharmaceutically acceptable nasal dosage form for nasally delivering systemically therapeutic levels of drug e.g., morphine to a warm blooded mammal." More specifically, the Office asserts that the '378 disclosure "teaches a 15mg/0.1mL solution (15%) of morphine at pH 4.5." (See, Paper No. 6, page 4, second full paragraph).

Applicants respectfully traverse the foregoing grounds of rejection set forth by the Office and submit that the invention of claims 1-5 and 7 are neither disclosed nor suggested by the Hussain et al. '378 patent (or corresponding WO publication).

Currently pending independent claim 1 recites a "pharmaceutical formulation for intranasal administration comprising morphine or pharmaceutically acceptable salt thereof at a pH from about 3.0 to about 7.0". A primary tenet of the Office's rejection of this claim is that the Hussain '378 disclosure allegedly teaches "a 15mg/0.1mL solution (15%) of morphine at pH 4.5." It is respectfully submitted that this is not an accurate interpretation of the Hussain '378 reference, for the following reasons.

As a preliminary matter, Applicants previously submitted comments regarding the inoperability of the Hussain '378 disclosure, including the alleged teachings regarding pH and concentration (see, Amendment submitted on October 25, 2000 and the accompanying Rule 132 Declaration of Dr. Charanjit R. Behl). The Office dismissed this evidence without substantive consideration, on the following stated grounds:

> Regarding the statement by Dr. Behl and the remarks about the operability of Hussain (US Patent 4,464,378), note that every patent is presumed valid (35 U.S.C. 282), and since (sic) that presumption includes the presumption of operability. See MPEP 716.07.

Applicants respectfully submit that the Office's dismissal of the evidence presented in Dr. Behl's Declaration, based on a purported presumption of validity, is improper. In particular, the section of the Patent Act cited by the Office (35 U.S.C. § 282) relates only to subject matter that is claimed in an issued U.S. Patent. Specifically, Section 282 of the Act reads:

> Each claim of a patent (whether in independent, dependent, or multiple dependent form) shall be presumed valid independently of the validity of other claims . . .. (emphasis supplied).

Accordingly, statements in a patent specification are not accorded any specific presumption of validity, except to the extent that they may embody subject matter set forth in the allowed claims of the patent. Notably, the claims of the Hussain '378 patent generically recite methods and formulations comprising, e.g.:

> [A]n analgesically effective amount of morphine, hydromorphone, metopon, oxymorphone, desomorphine, dihydromorphine, levorphanol, cyclazocine, phenazocine, 3-hydroxy-N-methyl-morphinan, lovophenacylmorphan, metazocine, nor-levorphanol, phenomorphan, nalorphine, nalbuphine, buprenorphine, butorphanol, levallorphan, or pentazocine, or a nontoxic pharmaceutically acceptable acid addition salt thereof . . ..

Thus, the claims of the '378 patent present an extensive laundry list of purportedly "analgesically effective" compounds. However, Hussain did not actually make a morphine solution as alleged by the Office (see further discussion below), and the claims of the '378 patent do not recite any particular pH or concentration of a nasal solution for any of the broad panel of listed drugs.

Therefore, the alleged teachings of Hussain '378 regarding pH and concentration of a nasal morphine solution are not entitled to a presumption of validity under 35 U.S.C. § 282, contrary to the Office's assertions. Considering the relevant subject matter, i.e., the '378 claims, no such presumption applies.

Even if the purported teachings of Hussain '378 relied upon by the Office were in fact entitled to a presumption of validity under 35 U.S.C. § 282 as alleged, which they are not, the Office must still consider all of the evidence presented in Dr. Behl's Declaration and further supplemented herein (see, accompanying Declaration of Dr. Steven C. Quay) in full, substantive detail. This evidence, and the scientific conclusions based thereon, must be viewed by the Office as presumptively correct, unless the Office provides validated evidence that is "inconsistent" with Applicants' evidence and conclusions. See, e.g., In re Marzocchi et al., 169 USPQ 367 (CCPA 1971).

Further, even if the presumption of validity accorded to the Hussain '378 disclosure by the Office was valid, Applicants need merely show by "a preponderance of the evidence" that the asserted teachings are inoperable (see, e.g., MPEP § 716.07, cited also by the Office). In the present case, the evidence of record is unequivocal that the alleged teachings of Hussain '378 regarding pH and concentration of an intranasal morphine solution cannot be practiced by the skilled artisan according to the Office's interpretation.

Briefly, the Office asserts that the protocol of Hussain '378 for making an aqueous nalbuphine hydrochloride solution (citing column 10, example 2) is a direct, operable teaching for preparing a "a 15mg/0.1mL solution (15%) of morphine at pH 4.5." However, Applicants submit that this interpretation of the disclosure is contrary to the understanding of the skilled artisan, and is scientifically ill-founded in many respects. Moreover, the asserted teachings are clearly invalidated by the evidence herein, on the basis that they would lead to an inoperable result.

As an initial point in rebuttal to the Office's position, the protocol of Hussain et al. for making a nalbuphine hydrochloride solution does not teach a final pH adjustment to a value of 4.5. Rather, the pH adjustment to 4.5 is conducted at an intermediate stage, prior to the addition of water to reach final volume, and prior to adjustment of tonicity. For these reasons, the reference cannot be aptly construed as teaching a final pH of any solution, particularly morphine sulfate. (See, Declaration of Dr. Steven C. Quay at ¶ 7).

Secondly, the Hussain '378 protocol for making a nalbuphine hydrochloride solution is not expressly taught as a useful protocol for preparation of a morphine sulfate solution. Rather, the nalbuphine hydrochloride protocol is speculatively disclosed by Hussain as a method that can be "substantially repeated" for making a morphine solution. As set forth in the accompanying Declaration of Dr. Quay (at ¶8):

> [T]he term "substantially repeated" leaves open all unspecified conditions and parameters of the protocol to routine adjustment, particularly modifications aimed at tailoring the protocol to the specific characteristics of substitute compounds proposed for formulation according to the general protocol (e.g., morphine sulfate, and pentazocine lactate, each proposed as substitutes for nalbuphine hydrochloride).

Given this open invitation to select alternate parameters and conditions, the Office must look to the skilled artisan for further construction of the Hussain '378 disclosure. In this regard, additional testimony provided in the Declaration of Dr. Quay (at ¶ 8) shows that:

> Among the most likely parameters that would be considered for change in this context is adjustment of pH for a morphine sulfate, versus nalbuphine hydrochloride, solution. Simply put, the artisan would not presume from the cited passage that the '378 disclosure teaches a final pH of 4.5 for a morphine sulfate solution, even if one accepts the Office's position that the passage actually teaches this value for a nalbuphine hydrochloride solution. On the contrary, the artisan would more likely interpret the express qualification conveyed by the term "substantially repeated" in the passage, to leave the protocol open to such desired modifications as compound-specific pH adjustment.

Considering this evidence further, the skilled artisan would <u>not</u> have followed the teachings of Hussain '378 in the manner proposed by the Office to select a pH for a morphine sulfate solution even close to the proposed value of pH 4.5. This conclusion is firmly grounded on the well known principal that a drug's ability to be delivered systemically across mucosal surfaces generally depends on the degree of ionization of the subject drug. As further described in the accompanying Declaration of Dr. Quay (at ¶ 9):

> It was widely understood at the time of the invention that the degree of ionization of a drug influences the drug's ability to be delivered systemically across mucosal surfaces. The degree of ionization of a particular drug is largely determined by the drug's dissociation constant, the pKa, and the pH of the solution in which the drug is

> dissolved (The pKa of an acid is equal to the pH at which half of the molecules are ionized and half are neutral). A basic drug would be mostly in its unionized state when dissolved in a solution having a pH greater than the pKa of the drug. Accordingly, basic drug formulations are believed to be best absorbed from alkaline solutions where the pH is greater than the drug's pKa. In the particular case of intranasal formulation chemistry, it was a widely known teaching in the art that basic drugs generally show improved absorption across the nasal mucosa into the bloodstream when they are formulated in a basic solution having a pH greater than the dissociation constant of the drug. Therefore, for morphine formulations where the subject drug is a basic drug having a pKa of about 8.0, the artisan would generally have predicted the drug to be best absorbed when formulated in a basic solution, wherein the morphine would be delivered predominantly in its unionized state. (emphasis supplied).

In accordance with this testimony, it is clear that, for morphine formulations where the subject drug is a basic drug having a pKa of about 8.0, the artisan would typically select a basic delivery solution as close to this value as possible to deliver the morphine predominantly in its unionized state. This direction, which contravenes the Office's position on a sound factual basis, is further explained in Dr. Quay's Declaration (at ¶ 10), as follows:

> Following this reasoning, the artisan would generally consider that solutions of morphine sulfate having a final formulation pH of greater than about 7.0 or 8.0 would allow for better absorption of morphine than lower pH solutions. For example, approximately 90% of the morphine sulfate in a solution having a final pH of about 9.0 would be expected to be in the preferred, unionized state (i.e., morphine free base). On this basis, such a high pH solution would be expected to provide for good absorption of morphine from the solution. In contrast, approximately 99% of the morphine would be predicted to be in an ionized state in a morphine sulfate solution having a pH of 6.0. A person of ordinary skill in the art generally would not have expected that morphine having such a high ionization level would provide for adequate absorption of the drug across the nasal mucosa into the bloodstream. The finding in the present invention that there is a high level of morphine absorption into the bloodstream when administered in formulations at pH 6.0 was therefore unexpected, and is clearly neither disclosed nor suggested by the art of record in the application. Similar results were shown for morphine sulfate at a pH range of about 3.0 to about 5.0, where over 99% of the morphine is also in an ionized state. (Uunderscores added).

The foregoing evidence incorporated in Dr. Quay's Declaration thus strongly refutes the prophetic teachings of Hussain '378, as they have been interpreted by the Office.

This evidence clearly demonstrates that the pH values and ranges claimed for an intranasal morphine solution in the present application represent "unexpected" results that general knowledge in the art prior to the invention taught directly away from.

It is also demonstrated in the Declaration of Dr. Quay, submitted herewith, that the alleged "substantially substituted" protocol of Hussain '378 can not be followed to yield a solution of morphine sulfate in the manner currently proposed by the Office. (See, Declaration of Dr. Steven C. Quay, at ¶¶ 11-12). Specifically, the Hussain protocol for nalbuphine hydrochloride teaches to combine 15 grams of nalbuphine hydrochloride with 80 mL of water, then to add enough sodium hydroxide solution to bring the pH of the composition to 4.5, then bring the solution to 100 mL with water. The Office itself notably concludes that the Hussain '378 patent teaches a morphine sulfate composition "containing 15 mg of morphine sulfate per 0.1 mL of water." The following testimony by Dr. Quay clearly evinces that this proposed formulation is inoperable:

> The statement in the '378 patent (Col. 10, Lines 45-49), that this procedure "is substantially repeated, except that 15 grams of morphine sulfate are used in place of the nalbuphine hydrochloride", *teaches an inoperable protocol*, and therefore cannot be interpreted in the strict manner proposed by the Office (Note: that the Office itself directly cites the Hussain '378 patent as teaching a morphine sulfate composition "containing 15 mg of morphine sulfate per 0.1 mL of water.") *The flaw in this interpretation of the '378 patent teachings is clearly revealed by the fact that the solubility of morphine sulfate in water would need to be at least approximately 150 mg/mL to achieve the formulation proposed by the Office* (by "substantial" substitution following the actual, nalbuphine hydrochloride procedure). *This solubility is grossly overestimated, and cannot be achieved under normal conditions at any pH. This defect is clearly elucidated by the following experiments* conducted under my direction and reported herein as follows: (italics added, underscores in original).

Dr. Quay's Declaration next provides detailed comparative experiments that in one part ("A") are directed to preparation of a morphine sulfate solution "Following Example 2 of U.S. 4,464,378 (as construed by the Office)." (Quay Declaration at ¶ 11). Specifically, 15

grams of morphine sulfate were mixed with 80 mL of water. The pH of the mixture was adjusted to 4.5 with dilute NaOH and stirred for two hours. The volume of the solution was made up to 100 mL with water. The results of this experiment are stated as follows:

> A clear solution was not obtained, indicating that 15 gm/mL of morphine sulfate is not soluble following the foregoing procedure, including intermediate adjustment of the 80 mL solution to pH 4.5.

The second experiment ("B") provided in Dr. Quay's Declaration (at ¶ 11) is directed to "Evaluation of Actual Solubility of Morphine Sulfate in an Aqueous Solution, Before and After pH Adjustment." To estimate the true drug solubility for morphine sulfate in an aqueous solution, the drug was added to water in small increments of about 0.5 gm each to obtain a saturated solution. After the solution was thus prepared, the volume of the solution was made up to 100 mL, and sufficient NaCl was added to adjust the solution to isotonicity. This procedure follows the Office's extrapolation of Example 2 of the '378 patent (directed to preparation of nalbuphine hydrochloride solution). The results of this experiment are stated as follows:

> Result: The characteristics of the saturated aqueous formulation at 80 mL were as follows:
>
> Water = 80 mL
>
> Morphine Sulfate added: 4.342 gm + 0.529 gm
>
> NaCl added: 0.218 gm (calculated based on total amount of Morphine Sulfate added.)
>
> These findings indicate that the estimated solubility of morphine sulfate in water is about 50 mg/mL.

In a final experiment, the pH of the saturated morphine sulfate solution prepared in experiment "B" above was adjusted to 4.5, in order to determine the effects, if any, that the pH adjustment would have on solubilization of the morphine sulfate (saturated as indicated at about 50 mg/mL in the non-pH-adjusted solution). To assess this factor, the pH of the solution was adjusted incrementally by slow, stepwise addition of NaOH. After each addition of

NaOH, the mixture was stirred for 30 min. (See, Declaration of Dr. Steven C. Quay, at ¶ 11). The result of this last experiment is stated as follows:

> Result: A clear solution of morphine sulfate from the solution set forth in subsection I), above, was not achieved at any elevated pH up to pH 8.12.

In light of these experimental findings, Dr. Quay aptly concludes in his Declaration (at ¶ 12) as follows:

> The foregoing experimental findings clearly demonstrate that the prophetic disclosure of the Hussain '378 patent regarding the preparation of a morphine sulfate solution (as strictly construed by the Office) is impracticable. This demonstration casts serious doubt upon all of the teachings of this reference pertaining to morphine formulations, including the desired pH of such formulations for intranasal use, as these teachings have been interpreted by the Office. *The prophetic suggestion to make a blanket substitution of morphine sulfate for nalbuphine hydrochloride in a slavishly copied protocol, which is contrary to the skilled artisan's interpretation of the disclosure for the reasons noted above, renders an inoperable formulation.* Because it is impossible to obtain a morphine sulfate solution "containing 15 mg of morphine sulfate per 0.1 mL of water", *there can be no valid scientific significance assigned to any disclosure of a particular pH value of such an impracticable solution.* (italics added, underscore in original).

In further consideration of the foregoing evidence, Dr. Quay additionally states in his Declaration (at ¶ 13) that "the skilled artisan would ordinarily have looked for additional information, in the patent and elsewhere in the art, to determine a desired pH for (an intranasal morphine) solution." In this context, Dr. Quay concludes that "the artisan would ordinarily have selected a considerably higher pH, e.g., greater than 7.0 or 8.0, in light of the knowledge summarized above concerning the pKa of morphine and the desirability of delivering drugs across mucosal surfaces in an unionized state."

Dr. Quay also critically points to conflicting teachings in the Hussain '378 patent that teach directly away from the intranasal morphine formulations (e.g., pH 4.5 and 150

mg/mL) proposed by the Office. In particular, the following quotation from the Hussain '378 disclosure (Example 5, at columns 11-12), is cited in his Declaration (at ¶ 13):

> The following are illustrative aqueous solutions of selected drugs suitable for use as nasal drops or nasal spray. In each case, the pH of the final composition is adjusted to 7.4 . . .. (emphasis added).

In ¶ 14 of his Declaration, Dr. Quay emphasizes that:

> The first identified composition in this Example ('COMPOSITION A') is an aqueous intranasal formulation of nalbuphine hydrochloride. The teaching that the final pH of this nalbuphine composition is to be adjusted to pH 7.4, rather than pH 4.5, is facially inconsistent with the Office's interpretation of the protocol described in Example 2 of this reference, discussed above, and is consistent with my conclusion that the teachings regarding pH adjustment in Example 2 fail to convey a desired final pH adjustment to 4.5—for either a nalbuphine or morphine intranasal formulation.

In summary, the evidence provided in Dr. Quay's Declaration and elsewhere in the record demonstrates clearly that the prophetic formulation method of Hussain '378, as construed by the Office, yields an inoperable result. The nature of this inoperable teaching relates to the solubility of morphine sulfate in aqueous formulations. To follow the '378 patent teachings for nalbuphine hydrochloride as advocated by the Office, the solubility of morphine sulfate in water would need to be at least approximately 150 mg/mL. As the data provided in Dr. Quay's Declaration clearly evince, this solubility is grossly overestimated, and cannot be achieved under normal conditions at any pH.

These experimental findings clearly demonstrate that the prophetic disclosure of the Hussain '378 patent regarding the preparation of a morphine sulfate solution (as construed by the Office) is "impracticable." If the skilled artisan were in fact motivated to attempt to achieve the 150 mg/mL morphine solution by "substantially" following the nalbuphine hydrochloride protocol, the attempt would necessarily be considered a failure (it is of course not possible to nasally administer a solution that is approximately three-fold over-saturated!) This fact, that it is facially impossible to obtain a morphine sulfate solution following the

disclosure of Hussain '378 for nalbuphine hydrochloride, indicates that there can be no valid scientific significance assigned to any disclosure of the reference regarding a particular pH value of an effective, intranasal morphine sulfate solution. On this basis, and for the other reasons set forth herein above, the rejection of claims 1-5 and 7 under 35 U.S.C. §102(b) as allegedly anticipated by Hussain et al. (WO 82/03768 or U.S. 4,464,378) is respectfully submitted to be overcome.

Claims 1-11 and 14-15 stand rejected under 35 U.S.C. §102(b) as allegedly anticipated by Merkus (5,756,483), for reasons stated in the prior office action. In a related rejection, claims 1-11, 14-15 and 32 are rejected under 35 U.S.C. §102(e) as allegedly anticipated by Merkus (5,942,251). Applicants respectfully traverse.

The Office contends that the Merkus references (U.S. Patents: 5,756,483 and 5,942,251) teach an effective, nasally-administered morphine composition having a specific pH of pH 6.0. However, the teachings of these two equivalent disclosures have not been properly construed by the Office.

As an initial point, the Office's reliance on the Merkus patents as any form of prior art reference in this application marks a clear procedural error. In particular, the teachings of Merkus that are relied upon by the Office are not in fact part of the disclosures of the cited patents. Instead, the subject teachings are expressly represented in the Merkus disclosures as a previous attempt by others (Verweij et al.) to formulate intranasal morphine. This cited Dutch study yielded undesired results, which are directly criticized and distinguished in the Merkus disclosures (column 6, lines 37-64 of '483 specification; column 6, line 62 to column 77, line 22 of '251 specification). Consequently, it appears that the Merkus references are relied on improperly as the source of the supposed teachings, when in fact the cited material is not a disclosure of Merkus, but is instead presented as a failed attempt by others that therefore teaches away from the presently claimed subject matter. Consequently, the cited disclosure is not properly of record. Moreover, taken in combination with the Merkus teachings, the disclosure clearly does not support the Office's position.

Even if the disclosure in the Dutch study (Verwiej et al.) cited in Merkus regarding pH of nasal morphine formulations was properly made of record, the teachings ascribed to this disclosure do not support the Office's interpretation. In particular, the Office asserts that:

> Merkus teaches a pharmaceutical solution formulation of morphine for nasal delivery employing a morphine pharmaceutical salt at a pH of 6 . . . .. See, e.g., column 6, lines 37-50 in US Patent number 5,942,251. (Office Action Paper No. 6, at p. 4, underscore added).

Contrary to this interpretation by the Office, the citation of the Dutch study by Merkus includes the notation "phosphate buffer (0.01 mol/L; pH 6.0)." As indicated in the accompanying Declaration of Dr. Steven C. Quay (at ¶ 18), "this notation specifies the pH of the phosphate buffer, not of the final formulation achieved by inclusion of the buffer." It is therefore improper to conclude from this notation that the Dutch study teaches any specific pH of a final morphine formulation for nasal administration as presently claimed. As stated by Dr. Quay, the referenced text "should not serve as a scientifically sound teaching relating to the pH of the final solution, only the buffer." (id.)

In addition to the foregoing facts, the disclosures of the Merkus '483 and '251 patents regarding the Dutch (Verweij et al.) study teach directly away from the presently claimed invention—by suggesting that oral morphine formulations are superior to "proposed" nasal morphine formulations in the Dutch study. In particular, the Merkus disclosure (at column 6, lines 60-64 of '483 patent) directly criticizes and distinguishes the results of the Dutch study, as follows:

> [T]he bioavailability of morphine after giving the nasal spray as described by Verweij and van Gijn is relatively low. After nasal absorption there is no first pass effect and therefore the nasal bioavailability should be higher than the oral. (underscores added).

Merkus additionally notes with skepticism that the bioavailability of morphine delivered intranasally according to the Dutch disclosure was even lower than the oral bioavailability (column 6, lines 54-62 of '483 patent). Accordingly, the Merkus disclosures

actually teach away from any disclosure in the Dutch reference regarding effective intranasal morphine solutions. This additional evidence is summarized in the Declaration of Dr. Steven C. Quay (at ¶ 20), as follows:

> Based on the Merkus disclosure, the proposed nasally-administered morphine composition (including an unspecified amount of a phosphate buffer with a pH of 6.0) yields a morphine bioavailability that is substantially lower than the bioavailability of orally-administered morphine, which would lead the artisan to administer morphine compositions orally, not nasally (underscore added).

Patentability Under 35 U.S.C. §103 (a)

Claims 12-13 are rejected under 35 U.S.C. §103 (a) as being unpatentable over Merkus (5,756,483) for reasons stated in the prior office action. Claims 30-32 are rejected under 35 U.S.C. §103 (a) as being unpatentable over Merkus (5,756,483) or Hussain et al. for reasons stated in the prior office action. The Merkus and Hussain references are cited as above for allegedly teaching a pharmaceutical composition of morphine for nasal delivery with an acidic pH in the range of Applicants claims.

Applicants remarks above, as supported by the accompanying Declaration of Dr. Steven C. Quay, obviate the stated grounds of rejection relating to the teachings of the Hussain and Merkus references. The same deficiencies of these references identified above in the context of the rejections under 35 U.S.C. § 102 are respectfully submitted to obviate the instant rejection of dependent claims 12-13, and 30-32, under 35 U.S.C. § 103.

CONCLUSION

In view of the foregoing, Applicants believe that all claims now pending in this Application are in condition for allowance and an action to that end is urged. If the Examiner believes a telephone conference would aid in the prosecution of this case in any way, please call the undersigned at 206-467-9600.

Respectfully submitted,

Dated: July 9, 2001

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